



Expert Interview with Dr. Nabih Ramadan

Highlights of the National Headache Foundation 7th Headache Research Summit

Introduction

The National Headache Foundation's 7th Headache Research Summit took place on October 16, 2009 in Chicago, Illinois as a satellite event of the annual meeting of the Society for Neuroscience. The summit invites basic, clinical, and translational researchers and clinicians to share and discuss recent advances in physiological, genetic, and clinical aspects of primary headache disorders. The morning session of the 7th Summit focused on the basic sciences of cephalic pain and migraine, while the afternoon session addressed clinical and applied sciences of headache disorders.

Dr. Nabih Ramadan, course co-director of the summit, was interviewed for *Migraine Resource Network* on December 29, 2009. His professional biography precedes the in-depth discussion about these discussions at the summit in addition to other recent observations and research discoveries in the area of headache disorder and migraine.

Biography

Nabih Manih Ramadan, MD, FAAN, FAHS
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Dr. Ramadan is currently chief medical officer of the Division of Developmental Disabilities, Nebraska Health and Human Services and clinical professor of neurology in the Department of Neurology at Loyola University in Chicago. Dr. Ramadan received his medical degree from the American University of Beirut College of Medicine, and completed a residency in neurology at the University of Cincinnati and a fellowship in cerebrovascular diseases at Henry Ford Hospital & Health System. Dr. Ramadan earned an MBA (Health Systems) with distinction from Keller Graduate School of Management.

Dr. Ramadan was presented with the Harold Wolff Award for best research on headache in 1989, was an NIH Javit Stroke Fellowship award recipient, and was honored twice as Faculty Teacher of the Year. He has authored or co-authored over 200 manuscripts, abstracts, book chapters, and editorials and co-edited the highly popular book *The Headaches*, 3rd Edition.

Dr. Ramadan's research interests include migraine, stroke, and chronic pain and he is in global demand as a speaker on topics related to headache, pain, stroke, clinical research, clinical trials methods, and neuropharmacology.



Interviewer

One of the educational goals of Summit 7 was to translate the value of electrophysiologic testing to improve headache medicine and improve understanding of cephalic pain. What is the value of the technology and how does the information obtained using electrophysiology differ from information obtained from positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)?

Dr. Ramadan

PET and fMRI are not electrophysiologic by design. Both modalities are considered forms of functional imaging of the brain. They are used primarily to understand the metabolic processes associated with the disease rather than aid in the diagnosis of the condition. Alternately, electrophysiologic testing is used for two main reasons. The first is to assist in the differential diagnosis of migraine and the second is to better understand disease mechanisms by exploring pathophysiologic processes, central effects of certain pharmacological treatments, and phenotype-genotype correlations. Of course each of these goals is achieved using different types of technologies. For example, electroencephalography or standard EEG is generally used to assist in the diagnosis of certain epileptic conditions with symptoms that look like migraine aura. Alternately, repetitive transcranial magnetic stimulation (rTMS or TMS) and electroencephalography (EMG) are both used towards gaining a better understanding of the mechanisms of migraine.

Interviewer

Can you please provide an example of how electrophysiologic testing has proved beneficial in obtaining a better understanding of mechanisms of migraine?

Dr. Ramadan

Data from multiple studies using facial EMG to track blink reflex in both migraineur and control populations have demonstrated significant habituation deficits in the migraineur group during migraine attacks and during the interictal period. The evidence suggests migraine brains are hardwired differently from brains in individuals with no history of migraine. Migraine brains are more excitable as seen by the blink reflex which tends to 'short-circuit,' which is abnormal. The migraine brain seems to possess an inability to filter normal sensory information which correlates with migraine-brain hyperexcitability. These converging observations strongly suggest a unique mechanism is at work in the migraine brain, one that evokes an increase in cortical and brain stem neural excitability which is expressed easily with minimal threshold.

Interviewer

Can facial EMG blink-reflex testing be used as a diagnostic marker of migraine?

Dr. Ramadan

No, it is not considered a reliable diagnostic marker and it is an expensive technology that is not widely available or covered by managed care; however, it is a reliable method for use during drug discovery testing. For example, if a drug modulates the blink reflex in an animal model, the drug will then be tested in a small number of humans. If



the same effect occurs, the results can be interpreted as more generalized, and this information will help in the design of subsequent human clinical trials. The primary application of this technology is to expose and differentiate disease mechanisms.

Interviewer

Have PET or MRI studies contributed any new information to researchers about metabolic processes of migraine?

Dr. Ramadan

Yes, a small French study out of CHU Rangueil in Toulouse was conducted by Gilles Géraud and colleagues with results published in August of 2009. Data from PET scans demonstrated posterior cortical hypoperfusion (reduced brain blood flow to the superficial brain layers in the back of the head) in patients during an attack of migraine *without* aura. We already know there is evidence of cortical spreading depression in patients with migraine *with* aura, but this study showed a reduction in blood flow during the migraine attack which persisted for many hours, long after the pain had been resolved by administration of sumatriptan, in patients *without* aura. These findings suggest a common mechanism, cortical spreading depression, may be at work in patients with migraine, despite the absence of visual aura.

Interviewer

Do the findings from the French study support the theory that migraine leads to an increase in white matter lesions?

Dr. Ramadan

The results do seem to suggest a correlation. Migraine attacks, with or without aura, appear to elicit a significant and extended vasodilatory shift, disrupting cerebrovascular homeostasis. Now, here is where MRI comes in...when cortical spreading depression occurs frequently and with sufficient intensity and duration, the associated vascular disruption is thought to be a causative factor of those small, multiple hyperintensities located in the deep or periventricular white matter that have been well documented on MRI scans acquired with T2-weighted or FLAIR sequences, displayed as areas of increased signal, in patients with migraine. It is theorized that recurring, sudden and significant shifts in vascular dynamics associated with cortical spreading depression may also contribute to an increased incidence and risk of stroke in patients with migraine. Questions and controversy surround these issues. We are still uncertain if the condition is caused by simply one factor of cortical spreading depression, for example the prolonged phase of hypoperfusion,* or if it is a result of the combined processes of cortical spreading depression and blood-brain barrier disruption. Is the initial hyperperfusion of the cortical spreading depression the trigger for blood-brain barrier disruption, or is it the response to blood-brain barrier disruption that initiates formation of subclinical white matter lesions? At this point, additional research is needed to differentiate the nuances of each process. We do acknowledge the fact that white matter lesions, those observed in the migraine brain, are similar to the ones we've seen

*Normal cerebral blood flow values are 50 to 54 milliliters (mL) of blood per 100 grams of brain tissue per minute, hypoperfusion values fall somewhere in the 20 mL/100 grams range and in ischemia, the range is significantly reduced, with cerebral blood flow decreased to between 5 to 10 mL of blood per 100 grams of brain tissue per minute.



in patients with stroke. But this statement of truth only stimulates more questions, rather than providing answers. Are all white matter lesions identical independent of disease state? Are the pathologic processes that are contributing to the lesions' formation unique? These and many other questions remain unanswered.

Interviewer

Did the summit offer any new insights regarding pain in patients with migraine?

Dr. Ramadan

Linda Watkins, a PhD professor of psychology, University of Colorado at Boulder, presented information from her team's research findings on the role of glial cell activation and subsequent release of neuroexcitatory and proinflammatory cytokines. Some of the agents that cause inflammation include calcitonin gene-related peptide (CGRP), C-reactive protein (CRP), interleukin 1 β (IL-1 β), nitric oxide (NO), substance P, neurokinin A, and tumor necrosis factor (TNF). In acute migraine, proinflammatory agents excite nerve endings and when inflammation occurs frequently, excitation is prolonged, the stimulation threshold is reduced, and allodynia develops as a common comorbidity. Allodynia occurs when the patient has a painful response to a stimulus that is not normally considered painful, such as exposure to touch. In some patients there is also a reduced analgesic response, especially to opioid drugs. This series of activities partially explains why some patients develop a tolerance to opioids. As the nerve endings become hyperstimulated, an effective therapeutic response is only possible when the dose is increased. At some point in the course of treatment when using numerous dose elevations, the opioid itself may actually increase the perception of pain rather than reduce it. This condition is termed opioid hyperalgesia. It is important for the practitioner to differentiate between drug dependence and hyperalgesia because as the patient becomes drug tolerant, drug dependence may also occur, and in a minority of patients, drug abuse, misuse, and addiction are also possible secondary outcomes. There are many instruments that may be used to assess patients at risk of opioid addiction. In patients who may be prescribed frequent or chronic opioid analgesics, risk assessment and monitoring are both highly recommended.

Interviewer

In light of these findings, will new forms of treatment be formulated to inhibit the proinflammatory response mechanism for improved pain relief of migraine?

Dr. Ramadan

By conducting research using spectroscopy partnered with SPECT or PET imaging, various substances can be tagged with a radionuclide and will demonstrate either an active or inhibitory response at the receptor site. These imaging technologies can also be used to map synaptic circuitry. Drug researchers have already used some of these data to develop new therapies designed to modulate the inflammatory process. A CGRP inhibitor for use in the treatment of migraine is currently in clinical trials. And with adequate interest and funding, I am sure similar inhibitors for other inflammatory agents or enhancers of protective processes will follow, such as an intervention designed to block or inhibit glial activity with a goal to improve analgesic effects associated with opioid therapy.



Interviewer

You mentioned using risk assessment when considering frequent or long-term opioid therapy to identify patients at high risk of addiction. What are your thoughts about routine assessment of sleep-wake disorders in patients with migraine?

Dr. Ramadan

Yes, I think it is important to specifically ask the patient with migraine about his/her sleep patterns. If the patient with migraine reports difficulties with falling asleep or maintaining sleep, or if the circadian rhythm is affected, I'd suggest using additional assessment tools to determine to what extent the lack of sleep has impacted the patient's ability to function. Several symptoms and signs warrant the consideration for polysomnography in patients with headache or migraine and include people who wake up frequently in the night with headache, people with excessive daytime sleepiness, patients with insomnia, who are overweight, and/or snore excessively. It is also important to see how the pattern of migraine fits within the pattern of the sleep-wake cycle. How do the two conditions correlate? Using a combined sleep/migraine diary or calendar will provide comparative data for review.

In the case of circadian rhythm disorder, it is of value to determine if the syndrome is delayed or advanced. Differentiation is obtained by obtaining a comprehensive sleep history from the patient and results from a sleep study. There is a genetic mutation in individuals with advanced sleep phase disorder that predisposes them to migraine. The migraine condition clusters in families affected with the mutation.

Even without genetic predisposition, the melatonin system plays a significant role in sleep, pain, and body mass and weight. In patients with migraine and sleep-wake disorders, both conditions need to be diagnosed and treated independently. Concurrent treatment of both conditions may offer some synergy, although evidence in this area is lacking.

Interviewer

Is there an association between increased body mass index (BMI) and migraine?

Dr. Ramadan

Dr. B. Lee Peterlin, assistant professor of neurology and assistant professor of pharmacology and physiology at Drexel University College of Medicine in Philadelphia, presented research findings at the summit about the association between increased adipose tissue, especially fat at the belly, and migraine. She reported that both male and female patients, ages 20 to 55, who had greater waist circumference had a significantly higher rate of migraine than those with smaller bellies. When data were controlled for total body obesity, the association no longer held true for migraine prevalence in men. The research also showed that total body obesity as measured by BMI is a risk factor for chronic migraine, but this finding cannot be extrapolated to migraine prevalence in the general population.



Interviewer

Can you please explain why fat would influence onset or frequency of migraine?

Dr. Ramadan

White adipose tissue, the main component of belly fat, plays a critical role as an energy store, but also as an independent neuroendocrine organ. The fat produces a number of active protein peptides, called adipokines, which include hormones such as leptin, adiponectin, visfatin, apelin, vaspin, hepcidine, chemerin, and omentin, all of which can produce either pro- or anti-inflammatory effects. The fat also produces another group of agents, the inflammatory cytokines, including tumor necrosis factor alpha (TNF), monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator protein (PAI).

We also recognize that estrogen and estrogen receptors are significant, as women are three times more likely than men to have migraine. Estrogen receptor alpha (ER-alpha) sites are prolific in white fat tissue. Both inflammation and 17 beta-estradiol can modulate ER-alpha expression. Additionally, estrogen is known to increase facial allodynia through activation of mitogen-activated protein kinase (MAPK) and extracellular-signal regulated kinase (ERK) in trigeminal ganglion neurons. Recent studies using rodent models have implicated ER-alpha and the novel estrogen receptor G-protein coupled receptor 30 (GPR30) as both playing a role in this process. These findings support earlier findings that have shown estrogen may either trigger onset of migraine and other types of pain involving the trigeminal nerve or may ameliorate these conditions. There are conflicting observations. We really need a comprehensive understanding of estrogen and its receptors, as well as to identify other neurochemicals that compete with estrogen for receptor activity to determine hormonal-receptor interplay, expression and cross talk. Further research in this area is needed.

The theory is that any one agent or a combination of proinflammatory agents can modify the cellular environment adequately to stimulate the lowered threshold of the migraine brain for onset of an attack. The flip side is that the environment, such as poor sleep, anxiety, depression, or pain, can trigger cellular release of inflammatory substances. The one fact that we can all agree on is that the brain is far more complex than previously imagined, impacted by a multiplicity of competing elements. Intercommunication between all organ systems and the brain is highly integrated, either vertically or horizontally, resulting in tremendous neurochemical agent and receptor cross talk. It is for these very reasons that research will unlikely provide one single effective universal therapy for migraine. There are far too many variables and multiple mechanisms involved.

Interviewer

At the summit, an entire presentation was dedicated to 'migralepsy.' Please define migralepsy and discuss its pathophysiology and clinical significance.

Dr. Ramadan

The condition of migralepsy is considered controversial. Migralepsy is a rare syndrome in which an individual has a migraine attack with aura and within one hour of migraine onset, a seizure will follow. These events lead to the assumption that migraine and



epilepsy may be sharing common features or pathways or at very least, beg the question: Does onset of migraine lower the threshold for seizure? Migraine and epilepsy appear to have a bidirectional relationship, yet migraine is more common in people diagnosed with epilepsy, while epilepsy is seen less frequently in people diagnosed with migraine with aura. Others believe that both migraine and epilepsy are distinct and unique conditions without shared pathophysiology. The important message to clinicians is be aware of these two comorbid conditions. If the patient presents with signs and symptoms that overlap both disorders, be sure to assess the patient for both conditions. Try not to favor the more serious of the two, the epilepsy, while ignoring the migraine syndrome. Selection of the safest and most effective treatment strategy will be based on the presence or absence of both conditions.

Interviewer

Most drugs for migraine prevention work by inhibiting the function of ion channels. What was reported at Summit 7 in regard to ionopathies?

Dr. Ramadan

Dr. Daniela Pietrobon presented results from a study conducted by her team at the University of Padova in Italy. They based their study on previous research that showed mice that carry the FHM1 mutation are more susceptible to cortical spreading depression.

Dr. Pietrobon reported that she and her colleagues found that calcium influx and subsequent glutamate release at cortical pyramidal cell synapses were increased in mice with the FHM1 mutation. Glutamate is the most common excitatory neurotransmitter in the brain, and in the experiments, induction and propagation of cortical spreading depression of the FHM mice population was completely eliminated when glutamate release was decreased to control levels. Of interest, despite enhanced excitatory neurotransmission, inhibitory neurotransmission was not altered. The synapse-specific effect of FHM1 mutations points to disruption of the balance between excitation and inhibition. It suggests neuronal hyperactivity as the causative agent that triggers cortical spreading depression which ultimately leads to migraine with aura.

These findings prompt interest in being able to modulate and control the activities at the synapse in order to maintain glutamate levels to inhibit excitation and reduce initiation of cortical spreading depression to control migraine. Proteomic research will focus on other ion channels, specifically sodium and potassium, to determine common and underlying mechanisms in regard to not only glutamatergic receptors, but GABAergic and vanilloid receptors and, as mentioned, taking a focused look at different proinflammatory cytokines, including IL-6 or TNF.

Interviewer

Dr. Ramadan, thank you for your time today to discuss Summit 7. We appreciate your expert insight.

Dr. Ramadan

You are most welcome!